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The risk of lung cancer with increasing time since ceasing exposure to asbestos and quitting smoking

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Objectives: To examine if the risk of lung cancer declines with increasing time since ceasing exposure to asbestos and quitting smoking, and to determine the relative asbestos effect between non-smokers and current smokers.

Methods: A cohort study of 2935 former workers of the crocidolite mine and mill at Wittenoom, who responded to a questionnaire on smoking first issued in 1979 and on whom quantitative estimates of asbestos exposure are known. Conditional logistic regression was used to relate asbestos exposure, smoking category, and risk of lung cancer.

Results: Eighteen per cent of the cohort reported never smoking; 66% of cases and 50% of non-cases were current smokers. Past smokers who ceased smoking within six years of the survey (OR = 22.1, 95% CI 5.6 to 87.0), those who ceased smoking 20 or more years before the survey (OR = 1.9, 95% CI 0.50 to 7.2), and current smokers (<20 cigarettes per day (OR = 6.8, 95% CI 2.0 to 22.7) or >20 cigarettes per day (OR = 13.2, 95% CI 4.1 to 42.5)) had higher risks of lung cancer compared to never smokers after adjusting for asbestos exposure and age. The asbestos effect between non-smokers and current smokers was 1.23 (95% CI 0.35 to 4.32).

Conclusion: Persons exposed to asbestos and tobacco but who subsequently quit, remain at an increased risk for lung cancer up to 20 years after smoking cessation, compared to never smokers. Although the relative risk of lung cancer appears higher in never and ex-smokers than in current smokers, those who both smoke and have been exposed to asbestos have the highest risk; this study emphasises the importance of smoking prevention and smoking cessation programmes within this high risk cohort.

Exposure to asbestos and tobacco smoking are known causes of lung cancer.[1 2] There is inconsistent information on the interaction between asbestos exposure and smoking and their joint impact on lung cancer risk. Some studies have suggested a multiplicative effect[3 4] (where the effect of asbestos exposure is a multiple of the effect of smoking, which has biological implications with regard to the multi-stage model of carcinogenesis), and meta-analyses have suggested that the additive model (where asbestos exposure and smoking are independent of each other) is unsound.[5 6] Yet others have shown that the effect of asbestos on lung cancer risk is greater in non-smokers than in smokers.[7] Liddell,[6] in a review of cohort studies, concluded that ''the relative risk of lung cancer from asbestos exposure is about twice as high in non-smokers as in smokers'', but Lee,[5] reviewing the same cohort studies and including case referent studies excluded by Liddell, concluded that the asbestos smoking interaction was multiplicative. Berry and Liddell,[7] using a modified measure, concluded that in non-smokers the excess relative risk of lung cancer from asbestos was about three times higher compared to smokers.

In former smokers, convergence towards the death and lung cancer risk of never smokers has been observed between 2 and 30 years after smoking cessation.[8–12] Little is known about the time span required for risk convergence in persons exposed to asbestos. Earlier work by de Klerk and colleagues[13] on Wittenoom workers, reported a convergence to near never smoking rates of lung cancer incidence (OR = 1.30, 95% CI 0.25 to 6.90) among those who had ceased smoking for 10 or more years.

Crocidolite (blue asbestos) was mined and milled at Wittenoom, in the remote Pilbara region of Western Australia, by the Australian Blue Asbestos Company (ABA) between 1943 and 1966. During that period 6493 men and 415 women[14] were employed, mostly for short periods of time (median 4 months).[15] Employment and dust exposure records obtained from ABA formed the basis of a cohort which has been under active follow up (at cancer and death registries and with periodic questionnaires) since 1975.[15–17]

The aims of this study were: (1) to determine if the risk of lung cancer reduces with increasing time since first exposure to asbestos and following smoking cessation; and (2) to examine the interaction between exposure to asbestos and smoking on lung cancer risk, among these former miners and millers.

METHODS

Participants

In 1979, 2928 former Wittenoom workers were traced and 2447 responded to a questionnaire on smoking and occupational histories.[13] Subsequent questionnaires in the 1980s and 1990s were returned by an additional 488 former Wittenoom workers to form a sub-cohort of 2935 (199 women and 2736 men). This represents 42% of the original ABA workforce.

Asbestos exposure assessment

Periodically between 1948 and 1958, measurements of dust concentrations were taken in the mine and the mill, by the Mines Department of Western Australia using a konimeter.[15] A survey of fibre counts using a Casella long running thermal precipitator was performed across the industry in 1966.[15] These measurements and the employment records provided by ABA, supplemented by records of contributions to a Mine Workers Relief Fund for workers prior to 1943, enabled the calculation of each former employee's cumulative exposure in fibre-years per ml, by adding over all their jobs the product of their estimated fibre concentration and the length of time in the job.

Table 1 Returned smoking questionnaires by year, and derived smoking status for cases and non-cases

Smoking questionnaires completed				
First survey year	**n (%)**	**Last survey year**	**n (%)**	
1979	2447 (83.4)	1979	829 (28.2)	
1982	202 (6.8)	1982	79 (2.7)	
1990–99	283 (9.6)	1990–1999	1401 (47.7)	
2000–01	3 (0.10)	2000/01	626 (21.3)	
Total	2935		2935	
	Cases	**Non-cases**	**Total**	
Smoking status*	**n (%)**	**n (%)**	**n (%)**	**p value**
Never	3 (2.2)	497 (19.2)	500 (18.3)	<0.001
Ex-smoker <6 years	11 (7.9)	46 (1.8)	57 (2.1)	
Ex-smoker 6–9 years	5 (3.6)	55 (2.1)	60 (2.2)	
Ex-smoker 10–19 years	20 (14.5)	308 (11.9)	328 (12.0)	
Ex-smoker 20+ years	8 (5.8)	656 (25.3)	664 (24.3)	
Current <20 per day	28 (20.3)	440 (16.9)	468 (17.1)	
Current ⩾20 per day	63 (45.7)	593 (22.9)	656 (24.0)	
Total	138	2595	2733	

*202 persons with incomplete smoking information were excluded.

Case ascertainment

Incident cases of lung cancer were determined from the Western Australian Cancer Registry up to September 2002 and the National Cancer Clearing House to September 2000. Lung cancer was identified using ICD-0 2nd edition categories C33.9–C34.9. Subjects were censored at their date of diagnosis of lung cancer, date of diagnosis of asbestosis, and date of diagnosis of malignant mesothelioma as well as date of death, September 2000 for non-Western Australian residents or September 2002 for West Australian residents, whichever was earliest.

Cases were matched randomly with up to 540 non-cases using the Stata 8.0 statistical package.[18] Non-cases were chosen if they were not known to have developed lung cancer, asbestosis, or mesothelioma by the year of diagnosis of the case, who were the same age (in five year age bands) and sex as the case, and who were known to be alive at the time of diagnosis of the case. Cases could be non-cases in years prior to the onset of their disease and subjects could be non-cases for more than one case.

Smoking information

Smoking status was sought from cohort members through questionnaires sent out between 1979 and 2000. At least one questionnaire was completed by 2935 people. Two hundred and two people returned incomplete questionnaires and therefore were not eligible for inclusion. Smoking information was updated by each subsequent questionnaire for those participants who completed more than one questionnaire. For participants who responded only to the 1979 questionnaire, their smoking status was assumed not to have changed throughout the study. For ex-smokers, the time since they had last smoked was assumed to be the time between giving up and the time of diagnosis of their disease, or disease of the matched case.

Ethics approval was obtained from the Human Research Ethics Committee of the University of Western Australia.

Statistical analysis

Age and time since stopping smoking were considered time dependent covariates and were advanced for each year of the study. Asbestos exposure variables were positively skewed and so were transformed to their natural logs. Conditional logistic regression using all eligible non-cases in the analyses (rather than a fixed number per case) so that information was maximised, was used to relate asbestos exposure, smoking status, and lung cancer. In order to adjust for possible bias resulting from subjects who stopped smoking because they developed a life threatening condition, we repeated the analysis excluding those who were diagnosed with a lung cancer within three years of stopping smoking (n = 6). We also examined whether the age that a subject stopped smoking impacted on the risk of lung cancer incidence. This analysis was restricted to those persons who reported an age at which they stopped smoking (n = 1109, 44 cases and 1065 non-cases). In order to determine the effect of asbestos exposure on lung cancer we calculated the relative asbestos effect (RAE).[19] This was derived from the odds ratio of non-smokers (never smokers and ex-smokers who ceased smoking 20 or more years ago)/odds ratio of current smokers.[6 19] The modified measure, RAE_m, which is the ratio of the excess risks, that is the ratio of the (OR−1)s, was also used.[7] All analyses were undertaken using Stata 8.0.[18]

Table 2 Characteristics of case and non-case subjects (138 cases and 2595 non-cases)

	Cases n (%)	**Non-cases n (%)**	**Total n (%)**	**p -value**
Male	132 (95.7)	2418 (93.2)	2550 (93.3)	0.182
	Mean (SD)	**Mean (SD)**	**Mean (SD)**	
Time since first asbestos exposure (years)	32.1 (8.6)	37.6 (7.1)	37.3 (7.3)	<0.001
Time since last asbestos exposure (years)	30.5 (8.7)	36.4 (7.6)	36.1 (7.8)	<0.001
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**	
Cumulative asbestos exposure (f/ml-year)*	9.2 (6.7–12.7)	5.5 (5.1–5.9)	5.7(5.3–6.0)	0.0011
Duration of exposure (days)*	195 (151–253)	139(131–147)	141 (134–149)	0.0086

*Geometric mean.

Table 3 Risk of lung cancer in 138 cases and up to 2595 matched non-cases per case, adjusting for time since first asbestos exposure, cumulative asbestos exposure, and smoking status

	OR	(95% CI)	p value
Time since first exposed (years)	0.84	(0.81–0.87)	<0.001
Cumulative exposure (log f/ml-year)	1.17	(1.05–1.30)	0.005
Never smoker	1.00		
Ex-smoker <6 years	22.1	(5.6–87.0)	<0.001
Ex-smoker 6–9 years	9.3	(2.2–40.1)	0.003
Ex-smoker 10–19 years	8.9	(2.6–30.1)	<0.001
Ex-smoker 20+ years	1.9	(0.50–7.2)	0.341
Current <20 per day	6.8	(2.0–22.7)	0.002
Current ⩾20 per day	13.2	(4.1–42.5)	<0.001

Min. non-cases = 7; max. non-cases = 494.

RESULTS

Most members of the cohort completed their first smoking questionnaire in 1979 (table 1). Of these, one third have not completed a further smoking questionnaire. Less than one fifth of the cohort were ''never'' smokers, fewer cases than non-cases. Approximately half of the cohort were current smokers at the time they completed their last questionnaire (two thirds of cases and almost half of non-cases). Of those who reported smoking at the time of their last questionnaire, more than half smoked more than 20 cigarettes a day (table 1).

Between 1979 and 2002 there were 138 incident cases of lung cancer in the cohort. Cases had a greater duration of exposure to asbestos and greater cumulative asbestos exposure than non-cases (table 2).

After adjusting for time since first asbestos exposure and cumulative asbestos exposure, the relative risk of lung cancer in subjects who had ceased smoking for 20 or more years by the end of follow up reduced so that it was not significantly greater than that of never smokers (table 3). The risk of lung cancer for those who had ceased smoking for six years or less was 22 times greater than those who never smoked. The risk of lung cancer was reduced in former smokers who had stopped smoking for more than six years. Current smokers had an increased risk of lung cancer compared to never smokers, with those who smoked 20 or more cigarettes a day having twice the risk of those who smoked less than 20 cigarettes a day.

Persons who stopped smoking aged 50 years or older (n = 25) had an increased risk of lung cancer (OR = 1.41, 95% CI 0.67 to 2.97) compared to those who ceased at younger ages (n = 19) (however this difference was not statistically significant).

After excluding those who developed lung cancer within three years of stopping smoking, the risk of lung cancer in former smokers who had stopped for six years or less reduced (OR = 16.3, 95% CI 3.5 to 76.1), but was still large compared to those who had stopped for 6–9 years (OR = 9.75, 95% CI 2.3 to 42.1), 10–19 years (OR = 8.9, 95% CI 2.6 to 30.3), or 20 or more years ago (OR = 1.91, 95% CI 0.5 to 7.2).

The asbestos effect was higher in never and ex-smokers than in current smokers (table 4).

DISCUSSION

We assessed the impact of smoking, smoking cessation, and exposure to asbestos on lung cancer risk in a cohort of former miners and millers of Wittenoom, exposed exclusively to crocidolite. In these people exposed to asbestos and tobacco but who subsequently quit smoking, the risk of lung cancer remained elevated up to 20 years or more after stopping smoking compared to never smokers. The risk of lung cancer in people who had stopped smoking for six years or less was 22 times the risk of never smokers. This attenuated when we excluded those who had been diagnosed with a lung cancer within three years of stopping smoking, but remained large compared to the other smoking categories. Current smokers remain at increased risk for lung cancer compared with never smokers. We did not find that age of smoking cessation impacted on subsequent risk of lung cancer incidence. The increased RAE in never and past smokers >20 years suggests that the effect of asbestos exposure may be greater in never and past smokers than in current smokers.

Thirty per cent of participants in this study answered their final smoking questionnaire in 1979. We assumed that their smoking status remained the same throughout the period of the study, 1979–2002. Of those who last responded in 1979, 38% reported being a former smoker at the time. It is possible that some of these resumed smoking subsequently. Of those who were current smokers at the time of their questionnaire, some are likely to have quit. Follow up studies may be more susceptible to misclassification than cross sectional studies,[11] especially in ''blue collar workers'',[20] as a result of the resumption of smoking among former smokers. This recidivism would lead to misclassification and either an under- or overestimation of our findings.[21] For current smokers who have quit, but in this analysis are considered as still smoking, misclassification could attenuate the estimate of the effect of current smoking on lung cancer incidence. Misclassification of those smokers who quit but subsequently relapsed would increase the estimate of the relative risk of former smokers. This may partly explain the substantially increased risk of lung cancer in persons who reported stopping smoking less than six years ago (in particular why the risk for this group is greater than for those who reported currently smoking). This increased risk reduced but was still substantial after excluding from the analysis those persons who were diagnosed with lung cancer within three years of smoking cessation.[11 22] A further explanation could be that those who reported not smoking in 1979 were in fact still smoking, and that ''social stigma'' encouraged them to report non-smoking. Taylor *et al* corrected for such misclassification and the estimate of the RR for current smokers increased by 8%.[21]

In contrast to other work,[10 21 22] this study shows no significant difference in health outcome among those who ceased smoking before or after the age of 50 years, although the difference is in the same direction and of the same order as in other studies.

Convergence towards the death and lung cancer rates of never smokers for former smokers has been inconsistent among persons not knowingly exposed to asbestos.[8–11] Wakai *et al* reported a convergence in deaths from lung cancer after 15 years of smoking cessation (RR = 1.29, 95% CI 0.46 to 3.63) among a cohort study of Japanese males aged 40–79,[8] while Enstrom reported a convergence in all causes of death (RR = 1.05, 95% CI 0.97 to 1.14) after 15 or more years and for deaths from lung cancer (RR = 1.73, 95% CI 0.93 to 3.22) after 15 or more years with follow up between 1954 and 1979

Table 4 Relative asbestos effect (RAE)

	Never smokers + ex-smokers >20 years Asbestos exposure		Smokers + ex-smokers <20 years Asbestos exposure	
	High	Low	High	Low
Cases	6	5	63	64
Controls	410	743	554	888
Relative risk				
OR (95% CI)	2.02 (95% CI 0.61–6.72)		1.64 (95% CI 1.124–2.37)	
Relative asbestos effect (NS:S) RAE	1.23 (95% CI 0.35–4.32)			
Modified asbestos effect (NS:S) RAE_m	1.59 (95% CI 0.12–20.50)			

among US veterans.[9] Peto *et al* found a reduced lung cancer risk (RR = 0.66) in men and (RR = 0.69) in women among those who had stopped smoking for less than 10 years.[10] After reviewing 10 case-control studies in Europe, Simonato *et al* found the risk for lung cancer in men was reduced to 66% of its value in continuing smokers for men after giving up smoking between two and nine years, 27% between 10 and 19 years, and 8% after more than 30 years since quitting smoking, compared with 4% for lifelong non-smokers. A possibility for recall bias and respondents exaggerating the time since they last smoked exists in this study as the time of quitting smoking was ascertained at an interview after diagnosis of lung cancer.[12] In former Wittenoom miners and millers exposed to both asbestos and tobacco, with follow up to 1986, de Klerk *et al* reported a statistically non-significant 30% increased risk in former smokers who had stopped smoking for 10 or more years compared to never smokers.[13] With longer follow up, this study reports a convergence for former smokers to the lung cancer incidence of never smokers to be 20 or more years. This longer time to risk convergence among persons exposed to both asbestos and tobacco may be due to the slower clearance of asbestos fibres from the lungs of smokers, especially those with impaired airway function, or slower clearance of tobacco by-products in subjects with excess asbestos fibres in their lungs.

In this study the asbestos effect was greater among never and ex-smokers (>20 years) than current smokers. Many previous researchers, including us, examining this issue have supported the hypothesis that the interaction between smoking and asbestos is multiplicative,[3 13] in that asbestos increases the risk in proportion to the effect of smoking.[6] Under the multiplicative hypothesis, the relative asbestos effect is the same in smokers and never smokers (RAE = 1), and a value greater than one indicates an interaction that is less than multiplicative. In our study the RAE was 1.23 and the RAE_m was 1.59, indicating that the interaction between smoking and asbestos exposure is less than multiplicative. Similar results have been found among chrysotile miners (RAE = 1.7, 95% CI 0.9 to 3.3)[23] and among a review of asbestos cohort studies (RAE = 2.04, 95% CI 1.28 to 3.25).[6]

Conclusion

In this cohort of former crocidolite miners and millers of Wittenoom, former smokers remain at an increased risk of lung cancer up to 20 or more years after ceasing smoking compared to never smokers. Although the relative risk of lung cancer appears higher in never and ex-smokers than in current smokers, those who both smoke and have been exposed to asbestos have the highest risk; this study emphasises the importance of smoking prevention and smoking cessation programmes within this high risk cohort.

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